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Original article

Trebananib (AMG 386) plus weekly paclitaxel with or without bevacizumab as first-line therapy for HER2-negative locally recurrent or metastatic breast cancer: A phase 2 randomized study

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ABSTRACT

Introduction: This phase 2 randomized study evaluated trebananib (AMG 386), a peptide-Fc fusion protein that inhibits angiogenesis by neutralizing the interaction of angiopoietin-1 and -2 with Tie2, in combination with paclitaxel with or without bevacizumab in previously untreated patients with HER2-negative locally recurrent/metastatic breast cancer.

Methods: Patients received paclitaxel 90 mg/m^2 once weekly (3-weeks-on/1-week-off) and were randomly assigned 1:1:1:1 to also receive blinded bevacizumab 10 mg/kg once every 2 weeks plus either trebananib 10 mg/kg once weekly (Arm A) or 3 mg/kg once weekly (Arm B), or placebo (Arm C); or open-label trebananib 10 mg/kg once a week (Arm D). Progression-free survival was the primary endpoint.

Results: In total, 228 patients were randomized. Median estimated progression-free survival for Arms A, B, C, and D was 11.3, 9.2, 12.2, and 10 months, respectively. Hazard ratios (95% CI) for Arms A, B, and D versus Arm C were 0.98 (0.61−1.59), 1.12 (0.70−1.80), and 1.28 (0.79−2.09), respectively. The objective response rate was 71% in Arm A, 51% in Arm B, 60% in Arm C, and 46% in Arm D. The incidence of grade 3/4/5 adverse events was 71/9/4%, 61/14/5%, 62/16/3%, and 52/4/7% in Arms A/B/C/D. In Arm D, median progression-free survival was 12.8 and 7.4 months for those with high and low trebananib exposure ($AUC_{ss} \geq 8.4$ versus < 8.4 mg·h/mL), respectively.

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Conclusions: There was no apparent prolongation of estimated progression-free survival with the addition of trebananib to paclitaxel and bevacizumab at the doses tested. Toxicity was manageable. Exposure-response analyses support evaluation of combinations incorporating trebananib at doses > 10 mg/kg in this setting.
Trial Registration: ClinicalTrials.gov, NCT00511459

Introduction

Two receptor tyrosine kinase pathways important in induction and regulation of tumor angiogenesis are the vascular endothelial growth factor (VEGF) and angiopoietin axes [1,2]. Angiopoietin-1 and -2 influence the vasculature by binding to the Tie2 receptor [2]. Although the VEGF and angiopoietin pathways are distinct, they interact [2] and simultaneous blockade of both pathways may improve inhibition of tumor growth compared with blocking either pathway alone [3–5].

Several studies have assessed bevacizumab (an anti-VEGF-A antibody) plus chemotherapy as first-line treatment for recurrent or metastatic HER2-negative breast cancer [6–9]. In the E2100 study, bevacizumab plus paclitaxel versus paclitaxel alone significantly improved progression-free survival (PFS; 11.8 versus 5.9 months, respectively; $P < 0.001$) and objective response rate (ORR; 36.9% versus 21.2%; $P < 0.001$) in the first-line setting [8]. However, there was no significant difference in overall survival (OS) between the two treatment groups (26.7 versus 25.2 months; $P = 0.16$). Improvements in PFS have also been reported for combinations of bevacizumab with other chemotherapy regimens as first-line therapy for metastatic disease [6,7,9]. Given these improvements in PFS, but lack of concomitant improvement in OS, there has been considerable recent debate regarding the role of bevacizumab in the treatment of metastatic breast cancer [10–12].

Trebananib is an investigational, intravenously administered peptide-Fc fusion protein that binds to and inhibits the interaction of angiopoietin-1 and -2 with the Tie2 receptor. Tumor xenograft studies with trebananib have shown that dual inhibition of angiopoietin-1 and -2 in the context of concurrent VEGF blockade results in significantly better efficacy than inhibiting either target alone [1,13]. In phase 1 monotherapy and chemotherapy combination studies in patients with solid tumors, trebananib demonstrated antitumor activity and a specific toxicity profile [14,15]. In a randomized, placebo-controlled phase 2 study of trebananib plus weekly paclitaxel, patients with recurrent ovarian cancer who received trebananib demonstrated prolonged estimated PFS compared with those who received placebo with evidence of dose–response and exposure-response effects [16,17]. Treatment was tolerable, with specific and manageable toxicities. The objectives of this study were to estimate the treatment effect of trebananib (as assessed by PFS) when administered in combination with paclitaxel with or without bevacizumab in first-line treatment of locally advanced or metastatic HER2-negative breast cancer.

Methods

Patients

Eligible women (≥18 years) had histologically or cytologically confirmed HER2-negative (expression ≤ 2+ by immunohistochemistry and/or negative by fluorescence in situ hybridization) adenocarcinoma of the breast with locally recurrent (not amenable to resection with curative intent) or metastatic disease for which they had not been previously treated. Additionally, patients had Eastern Cooperative Oncology Group (ECOG) status ≤ 1; measurable/nonmeasurable disease per modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 [18], complete computed tomography (CT) or magnetic resonance imaging (MRI) scans and whole-body bone scintigraphy ≤ 28 days before randomization; and adequate hematologic, renal, hepatic, and cardiac function. Key exclusion criteria were inflammatory breast cancer; central nervous system metastasis; adjuvant/neoadjuvant taxane treatment within 1 year; prior radiation therapy, radiofrequency ablation, percutaneous cryotherapy, or hepatic chemoembolization ≤ 14 days before randomization; grade > 1 peripheral neuropathy; uncontrolled hypertension; history of arterial or venous thrombosis within 1 year; bleeding diathesis within 6 months; and previous treatment with VEGF or angiopoietin axis inhibitors. Patients provided written informed consent; study procedures were approved by an independent ethics committee/institutional review board at each center.

Study design and treatment

This was a randomized, placebo-controlled, 4-arm, multicenter (70 sites in four countries), phase 2 estimation study. Patients received intravenous (IV) paclitaxel 90 mg/m^2 once weekly (QW; 3-weeks-on/1-week-off) and were randomly assigned 1:1:1:1 to receive trebananib 10 mg/kg QW plus bevacizumab 10 mg/kg IV every 2 weeks (Q2W; Arm A), trebananib 3 mg/kg QW plus bevacizumab 10 mg/kg IV Q2W (Arm B), placebo plus bevacizumab 10 mg/kg IV Q2W (Arm C), or trebananib 10 mg/kg QW (Arm D). The doses of trebananib used in this study were selected based on pharmacokinetic analysis from the first-in-human monotherapy study. A maximum-tolerated dose was not reached in that study but doses greater than 3 mg/kg QW provided trough concentrations that were above the optimal biologic dose for tumor xenograft growth inhibition [1,14]. Treatment in Arms A, B, and C was double-blind; treatment in Arm D was open-label. Randomization was stratified by adjuvant taxane exposure (yes/no) and number of metastatic sites (≤3/>3). Treatment continued until disease progression, unacceptable toxicity, or withdrawal of consent. Doses of trebananib, bevacizumab or paclitaxel could be withheld according to protocol-specified rules. Doses of paclitaxel could be reduced to 65 mg/m^2 in the event of toxicity; dose modifications for trebananib and bevacizumab were not permitted.

The primary endpoint was PFS, defined as the time from randomization to disease progression (per RECIST) as assessed by investigators, or death. Secondary endpoints included ORR (confirmed complete response + partial response), duration of response (DOR), OS, time to response, incidence of adverse events (AEs), anti-trebananib antibody formation, and pharmacokinetics of trebananib.

Efficacy assessments

CT/MRI were performed at baseline and every 8 ± 1 weeks thereafter. Tumor response was assessed according to RECIST version 1.0 [18]. Patients who discontinued treatment without

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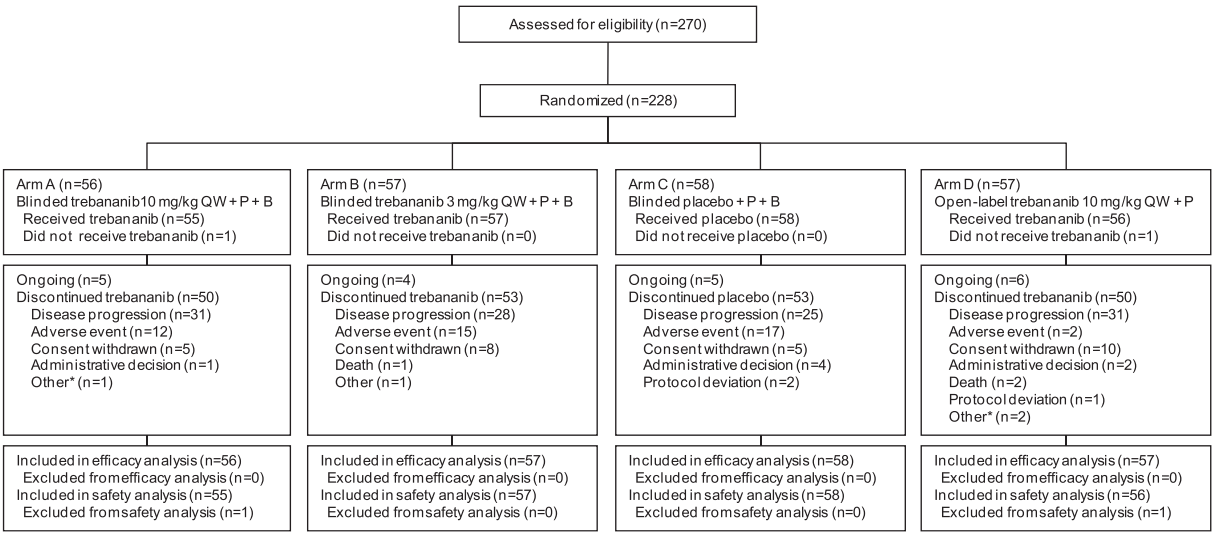

Fig. 1. Disposition of patients in the study. B = bevacizumab; P = paclitaxel. *Includes determination of ineligibility and lost to follow-up.

evidence of progression continued to have radiologic assessments every 8 ± 1 weeks until disease progression or initiation of new treatment. Long-term follow-up continued for 48 months (from the date the last patient was randomized).

Adverse events and immunogenicity

AEs occurring from study day 1–37 days after the last dose of study medication were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 3.0. Serum samples were collected predose on day 1 of cycles 1 to 3, day 15 of cycle 6, and every 16 weeks thereafter for the measurement of anti-trebananib binding and neutralizing antibodies as previously described [14].

Pharmacokinetic and exposure-response analyses

Serum samples were collected postinfusion at weeks 1, 5, and 15 to assess the maximum observed concentration (C_{max}) and pre-infusion at weeks 1, 3, 5, 9, 15, and every 8 weeks thereafter to

Table 1
Baseline demographics and clinical characteristics.

	Arm A Trebananib 10 mg/kg QW + Paclitaxel + Bevacizumab $n = 56$	Arm B Trebananib 3 mg/kg QW + Paclitaxel + Bevacizumab $n = 57$	Arm C Placebo + Paclitaxel + Bevacizumab $n = 58$	Arm D Trebananib 10 mg/kg QW (Open-Label) + Paclitaxel $n = 57$
Race/ethnicity, %				
White	80	96	83	91
Asian	13	4	10	7
Black	2	0	3	2
Hispanic	4	0	2	0
Other	2	0	2	0
Median (range) age, *y*	56.5 (32–75)	56 (26–83)	51.5 (31–74)	52 (27–76)
ECOG performance status, %				
0	61	67	60	70
1	38	33	40	30
2	2[a]	0	0	0
Median (range) time since primary diagnosis, mo	50.3 (1–152)	35.9 (0–242)	47.4 (0–300)	40.4 (0–180)
Stage IV disease at initial diagnosis, %	18	23	21	21
Metastatic sites, %				
≤3	79	77	79	72
>3	21	23	21	28
Sites of disease, %				
Liver	43	54	45	44
Lung	39	42	31	42
Bone	63	63	62	54
Estrogen receptor/progesterone receptor status, %				
Positive	80	82	78	65
Negative	18	18	21	33
Unknown	2	0	2	2
HER2/neu–negative disease status, %	98[a]	100	100	100
Triple-negative status, %[b]	16	18	21	32
Unknown	4	0	2	4
Adjuvant taxane treatment, %	18	21	19	16

[a] Protocol violation (one patient was HER2/neu–positive).
[b] Defined as negative for estrogen receptor, progesterone receptor, and HER2/neu (no amplification by FISH/CISH or 0/1 + by immunochemistry).

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assess the minimum observed concentration (C_{min}). Serum trebananib concentrations were measured as previously described [14]. In pharmacokinetic/pharmacodynamic analyses, Cox regression models were used to evaluate the effect of the area under the concentration–versus–time curve at steady state (AUC_{ss}) on PFS [16]. The cut-point for trebananib high versus low exposure (AUC_{ss}) in patients who received blinded trebananib (Arms A or B) was based on the median AUC_{ss} in Arm A; the cut-point in the open-label treatment arm (Arm D) represented median AUC_{ss} in that group.

Statistical analysis

A study size of 220 patients (n = 55/arm) was planned. Assuming median PFS of 11 months in Arm C and 16.9 months in Arms A and B combined (54% relative increase), the target event goal of 110 PFS events (68 in Arms A/B combined and 42 in Arm C), would allow estimation of the PFS hazard ratio (HR) for Arms A and B relative to Arm C with a two-sided confidence interval $\leq$ 0.34, assuming an observed HR of 0.65. The primary analysis was conducted using the all-randomized analysis set. Patients were analyzed according to treatment randomization, regardless of treatment received (intent to treat). Analyses of ORR, DOR, time to response, and reduction in tumor burden included patients with $\geq$1 unidimensionally measurable lesion at baseline. Safety analyses were conducted for all randomized patients who received $\geq$1 dose of trebananib, bevacizumab, or paclitaxel analyzed according to treatment received.

For analyses of PFS, a Cox regression model stratified by the randomization strata was used to estimate the HR and corresponding CIs for Arms A, B, and D individually, and for Arms A and B combined, versus Arm C [19]. Log-rank tests stratified by the randomization factors were used to evaluate differences in PFS for each comparison; P values were descriptive. Kaplan–Meier medians and two-sided 95% CIs were derived for time-to-event analyses [20]. Tarone's test, stratified by the randomization factors, was

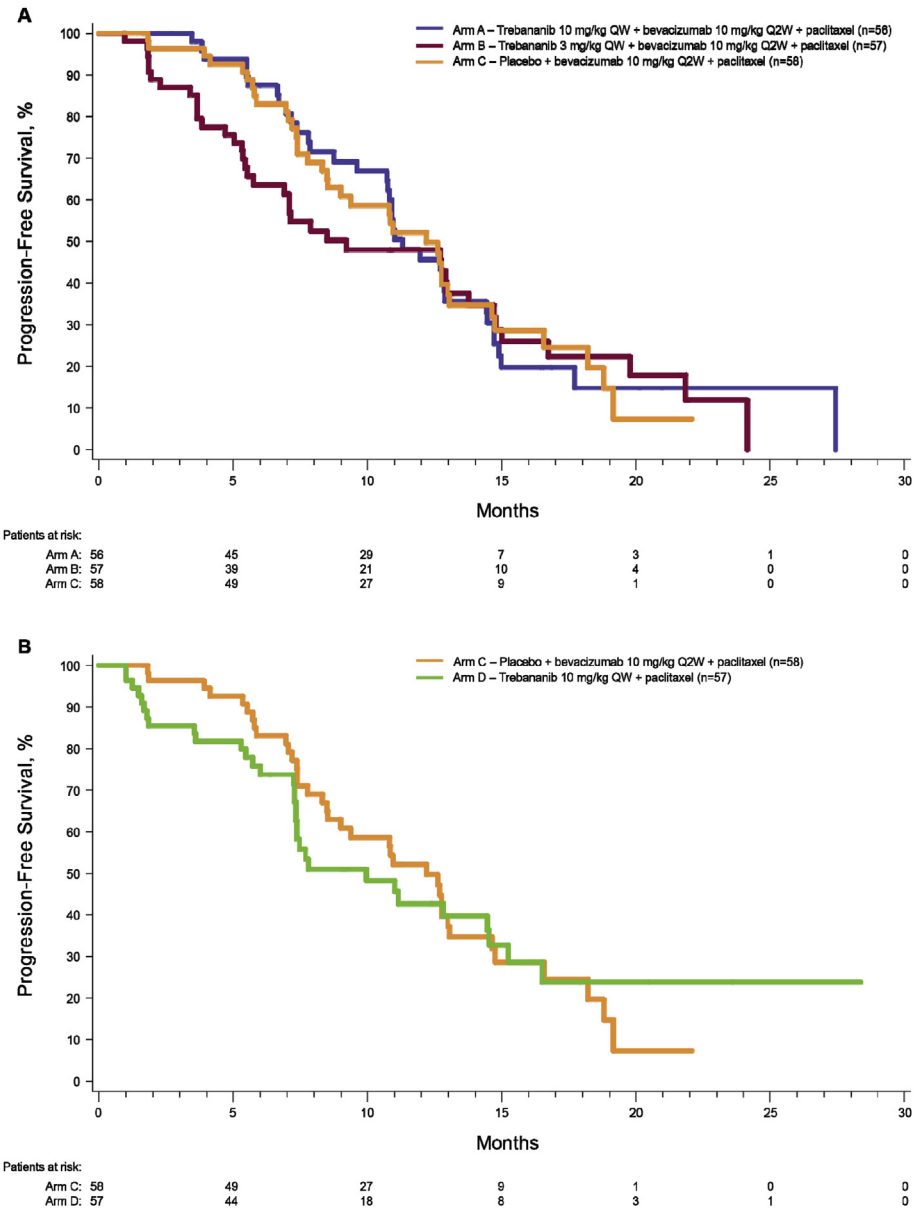

Fig. 2. Progression-free survival. Kaplan–Meier plot of progression-free survival among patients in (**A**) Arms A, B, and C and (**B**) Arms C and D.

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used to assess any trend in PFS across Arms A, B, and C. For each treatment arm, and for Arms A/B combined, exact binomial two-sided 95% CIs were generated for ORR. Wilson's score method with continuity correction was used to calculate 95% CIs for between-arm differences in ORR. Efficacy analyses were not adjusted for multiple comparisons.

Results

Patients

Two hundred and twenty eight patients were randomized (Fig. 1). Demographics and baseline characteristics were generally well balanced among treatment arms (Table 1). However, the percentage of patients with >3 sites of metastatic disease or triple-negative status was higher in Arm D than in other arms. Median time from primary diagnosis was 50.3, 35.9, 47.4, and 40.4 months for Arms A, B, C, and D, respectively. The median number of administered trebananib/placebo cycles was 9, 6, 9 and 8 in Arms A, B, C and D, respectively; the median number of administered bevacizumab cycles was 9, 6 and 8.5 in Arms A, B and C, respectively. In each arm, patients received a median of 6 cycles of paclitaxel with a mean (SD) relative dose intensity of 0.8 (0.1). Median (range) follow-up time for all patients was 66.4 (1–124) weeks.

Progression-free survival

Median PFS was 11.3, 9.2, 12.2, and 10.0 months in Arms A, B, C, and D, respectively (Fig. 2). Pairwise comparisons of each arm versus Arm C yielded an HR of 0.98 (95% CI, 0.61–1.59; $P = 0.95$) for Arm A, 1.12 (0.70–1.80; $P = 0.64$) for Arm B, and 1.28 (95% CI, 0.79–2.09; $P = 0.31$) for Arm D. The HR for Arms A and B combined versus Arm C was 1.05 (95% CI, 0.70–1.57; $P = 0.83$). There was no evidence of a dose–response effect. In an ad hoc analysis, median estimated PFS was shorter among triple-negative patients in all four treatment arms compared with patients positive for ≥1 receptor (Arm A, 7.4 versus 12.0 months; Arm B, 5.3 versus 12.7 months; Arm C, 8.4 versus 12.6 months; Arm D, 7.3 versus 11.1 months). OS data were not mature at the time of this analysis and are not reported.

Objective response rate

Most patients had measurable disease at baseline (Table 2). Confirmed ORRs in Arms A, B, C, and D were 71%, 51%, 60%, and 46%, respectively. Median time to response was longer and duration of response was shorter in Arm D than in the other three arms (Table 2).

Pharmacokinetic/pharmacodynamic analyses

The pharmacokinetics of trebananib were dose proportional when administered in combination with bevacizumab and/or paclitaxel and consistent with those reported previously [14]. At steady state, median trebananib C_{max} (week 5) was 260, 79.0, and 270 μg/mL in Arms A, B and D, respectively. Median trebananib C_{min} at steady state (weeks 5, 9, 15, and thereafter) ranged from 13.5–15.2, 3.36–4.20 and 13.8–18.0 μg/mL in Arms A, B, and D, respectively.

An exploratory analysis investigated the relationship between trebananib exposure and response. Patients in Arm A or B who had $AUC_{ss} \geq 9.1$ mg·h/mL (high exposure; $n = 29$) had a median PFS of 14.5 months (HR versus placebo, 0.72 [95% CI, 0.40–1.30]; $P = 0.28$); those with $AUC_{ss} < 9.1$ mg·h/mL (low exposure; $n = 83$) had a median PFS of 9.6 months (HR versus placebo, 1.22 [95% CI, 0.80–1.85]; $P = 0.36$; Fig. 3A). In Arm D, median PFS in the high ($AUC_{ss} \geq 8.4$ mg·h/mL, $n = 28$) and low ($AUC_{ss} < 8.4$ mg·h/mL, $n = 28$) exposure groups was 12.8 and 7.4 months, respectively (HR high versus low, 0.67 [95% CI, 0.32–1.37]; $P = 0.27$; Fig. 3B). In the blinded arms, ORR in the high-exposure group was 95% compared with 51% in the low-exposure group.

Adverse events

Incidence of grade ≥ 3 AEs was similar in Arms A (84%), B (81%), and C (81%) but was lower (63%) in Arm D (Table 3). In the four treatment arms (A, B, C, and D), 27%, 40%, 36%, and 30% of patients,

Table 2
Efficacy.

	Arm A Trebananib 10 mg/kg QW + Paclitaxel + Bevacizumab $n = 56$	Arm B Trebananib 3 mg/kg QW + Paclitaxel + Bevacizumab $n = 57$	Arm C Placebo + Paclitaxel + Bevacizumab $n = 58$	Arm D Trebananib 10 mg/kg QW (Open-Label) + Paclitaxel $n = 57$
Progression-free survival (PFS)[a]				
Patients with events, %	64	67	64	56
Median (95% CI) Kaplan–Meier PFS time, mo	11.3 (10.7–14.4)	9.2 (6.9–13.8)	12.2 (8.5–13.0)	10.0 (7.3–14.5)
Cox regression model				
PFS vs Arm C, HR (95% CI)	0.98 (0.61–1.59)	1.12 (0.70–1.80)		1.28 (0.79–2.09)
P	0.946	0.642		0.314
PFS Arms A + B vs Arm C, HR (95% CI)	1.05 (0.70–1.57)			
P	0.830			
Tarone test, *P*	0.580			
Confirmed objective response				
Patients with measurable disease at baseline, *n* (%)	41 (73)	49 (86)	42 (72)	46 (81)
Best confirmed response, %				
Complete response	7	2	0	4
Partial response	63	49	60	41
Stable disease	24	27	31	30
Progressive disease	2	10	5	13
Unevaluable[a]	2	6	0	2
Not done	0	6	5	9
Confirmed objective response rate, % (95% CI)	71 (55–84)	51 (36–66)	60 (43–74)	46 (31–61)
Median (range) time to response, weeks	8.0 (7.0–48.0)	8.1 (7.0–34.6)	8.7 (7.0–55.7)	15.3 (6.9–32.0)
Median (95% CI) duration of response, weeks	41.6 (24.0–55.0)	48.0 (24.0–64.9)	39.0 (29.1–47.9)	32.0 (23.7–56.0)

[a] Includes patients with an assessment of complete response, partial response, or stable disease before the first scheduled assessment with no additional assessment.

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respectively, had serious AEs (mostly vomiting, neutropenia, and pyrexia); 73%, 67%, 67%, and 43% had grade ≥ 3 AEs deemed related to any of the administered study treatments; and 16%, 23%, 16%, and 4% had AEs leading to permanent treatment or study discontinuation. Overall, there were no apparent dose-related trends in the incidence of AEs. Most of the deaths that occurred on study (Arm A, $n = 17$, Arm B, $n = 21$; Arm C, $n = 14$; Arm D, $n = 12$) were attributed to disease progression. Two patients had fatal AEs that were considered by the investigators to be possibly related to trebananib/bevacizumab (hemoptysis in Arm B) or paclitaxel (diarrhea and respiratory failure in Arm B).

Among AEs of interest, edema (Table 4) and specifically peripheral edema (Table 3) occurred more frequently in Arms A, B, and D than in Arm C, with few incidences of grade 3 events (no grade 4 or 5 events occurred). Hypertension and hemorrhagic events were reported more often in Arms A, B, and C than in Arm D. There was one incidence of grade 4 rectal hemorrhage and one of grade 5 hemoptysis in Arm B. Other noteworthy AEs included one arterial thromboembolic event (grade 4 myocardial infarction in Arm C), one gastrointestinal perforation (grade 3, Arm B), and one perirectal abscess (grade 2, Arm C). In some treatment arms, ascites, pleural effusion, and/or blurred vision occurred (all were grade 1 or 2 with the exception of one grade 3 pleural effusion in Arm B). These AEs have recently been identified as specific risks associated with trebananib treatment.

Overall, 220 patients had postbaseline immunoassay samples. In the trebananib treatment arms combined, 13/156 patients developed anti-trebananib binding antibodies; these were transient in all but three patients. No trebananib neutralizing antibodies were detected.

Discussion

In this phase 2 randomized study in patients with HER2-negative recurrent or metastatic breast cancer, we evaluated the estimated treatment effect on PFS of paclitaxel plus bevacizumab

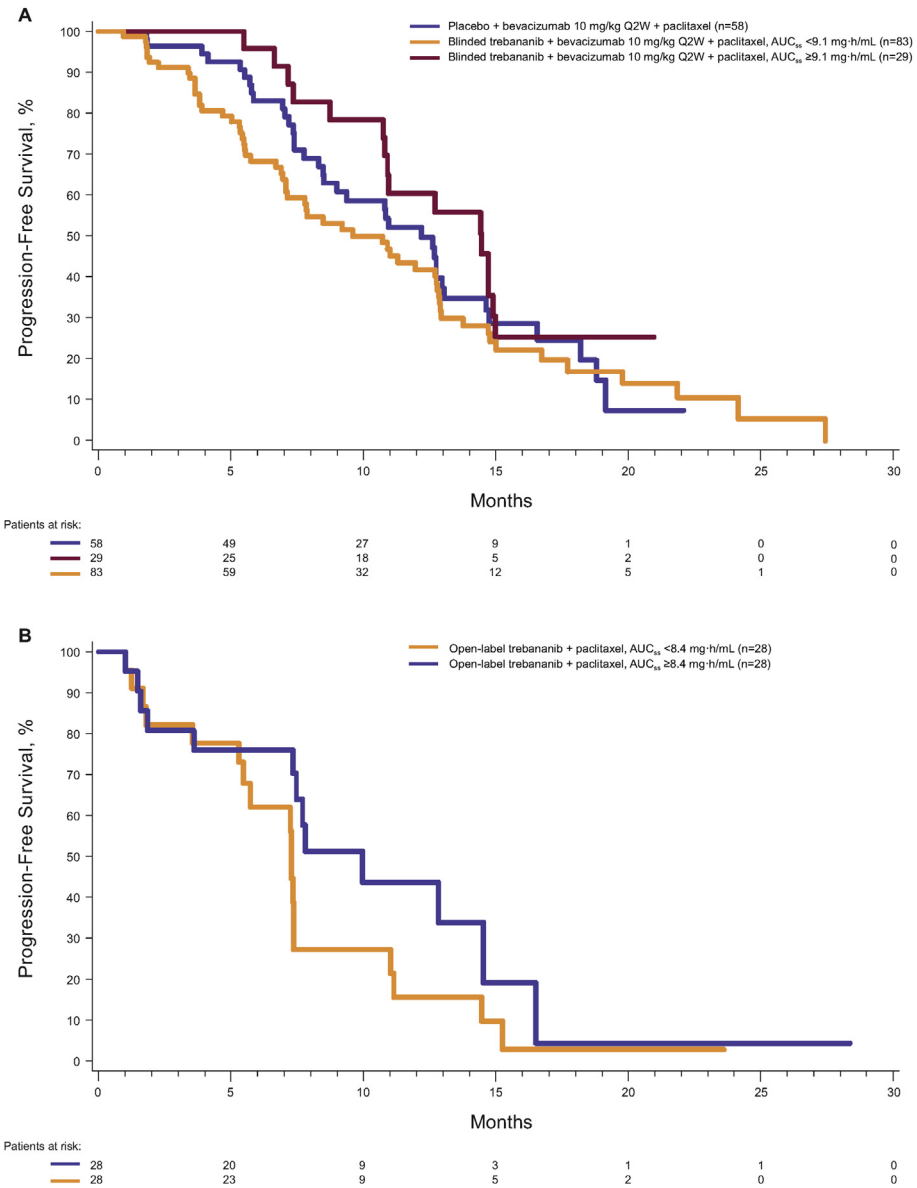

Fig. 3. Relationship between trebananib exposure and progression-free survival. Kaplan–Meier plots of progression-free survival among patients in (**A**) Arms A and B and (**B**) Arm D stratified by trebananib AUC_{ss}.

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Table 3
Incidence of adverse events.

	Arm A Trebananib 10 mg/kg QW + Paclitaxel + Bevacizumab $n = 55$	Arm B Trebananib 3 mg/kg QW + Paclitaxel + Bevacizumab $n = 57$	Arm C Placebo + Paclitaxel + Bevacizumab $n = 58$	Arm D Trebananib 10 mg/kg QW (Open-Label) + Paclitaxel $n = 56$
Patients with any adverse event, %	100	100	100	100
Grade 3	71	61	62	52
Grade 4	9	14	16	4
Grade 5	4	5	3	7
Adverse events (all grades) occurring in ≥30% of patients in ≥1 treatment arm, %				
Alopecia	64	61	60	55
Nausea	62	42	45	46
Epistaxis	44	61	50	18
Fatigue	49	58	38	27
Diarrhea	49	56	62	32
Peripheral edema	36	46	19	55
Headache	25	42	47	29
Constipation	24	42	36	23
Hypertension	40	39	38	13
Neutropenia	35	39	41	32
Peripheral neuropathy	35	39	28	38
Arthralgia	27	39	28	23
Vomiting	35	37	29	20
Nail disorder	36	35	24	9
Asthenia	31	33	33	39
Cough	31	26	34	32
Dysgeusia	31	18	31	16
Dysphonia	20	14	33	5
Grade ≥ 3 adverse events occurring in ≥5% of patients in ≥1 treatment arm, %				
Hypertension	18	23	19	4
Neutropenia	18	19	28	18
Peripheral neuropathy	20	7	10	11
Fatigue	5	9	2	2
Peripheral sensory neuropathy	5	7	2	4
Asthenia	7	4	5	5
Diarrhea	4	7	3	0
Alopecia[a]	4	7	0	5
Deep vein thrombosis	5	2	0	0
Nausea	2	5	2	2
Vomiting	2	5	2	0
Peripheral edema	2	4	2	5
Back pain	0	5	3	0
Aspartate aminotransferase increased	0	5	2	0
Leukopenia	2	2	3	5
Syncope	2	2	0	5

[a] Incorrectly reported as grade ≥ 3 by investigators.

with or without trebananib and also evaluated PFS among patients receiving trebananib plus paclitaxel. There was little evidence of improvement in estimated PFS or ORR among patients receiving blinded trebananib in combination with bevacizumab at the doses tested compared with blinded placebo plus bevacizumab. The estimated median PFS of 10.0 months and ORR of 46% in the open-label trebananib plus paclitaxel arm were not better than what was observed with placebo plus bevacizumab and paclitaxel treatment.

Median PFS for patients in the placebo arm was consistent with median PFS reported for patients receiving bevacizumab plus paclitaxel in other randomized studies (range, 8.8–12.9 months) [8,21,22]. ORR among patients in Arms A (71%), B (51%), and C (60%) was higher than previously reported for bevacizumab plus paclitaxel (range, 32%–52%) [8,21–23]. There were some imbalances in baseline disease characteristics (including the proportion of patients who had triple-negative status for which the analyses of efficacy were not adjusted).

Pharmacokinetic/pharmacodynamic analyses of patients with higher exposure to trebananib support further evaluation of trebananib at doses > 10 mg/kg in metastatic breast cancer. In Arm A, median PFS was longer among patients with $AUC_{ss} \geq 9.1$ mg·h/mL, and in Arm D median PFS was longer among patients with $AUC_{ss} \geq 8.4$ mg·h/mL. ORR was also improved among patients in Arms A and B who had high trebananib exposure (with a remarkable ORR of 95%), but there was no evidence that trebananib exposure influenced ORR in Arm D. Data from these exposure-response analyses must be interpreted cautiously given outcomes among patients in Arms A and B with high trebananib exposure were unadjusted for confounding factors and only moderately improved compared with patients in the placebo arm, and the lack of a control group for Arm D. Furthermore, data from this small estimation study did not demonstrate a dose–response for efficacy in the blinded treatment arms, and the exposure-response results from the blinded arms should be interpreted in that context. Of note, exposure-response analysis of a phase 2 study in patients with recurrent ovarian cancer produced a similar finding and supported use of trebananib at 15 mg/kg QW plus weekly paclitaxel in phase 3 studies [16]. In the phase 3 TRINOVA-1 study, treatment with trebananib 15 mg/kg QW plus weekly paclitaxel resulted in a significant improvement in PFS compared with placebo plus paclitaxel (HR, 0.66, 95% CI, 0.57–0.77, $P < 0.0001$) [24]. Trebananib is being investigated at doses up to 30 mg/kg in combination with chemotherapy and HER2-inhibitors in a phase 1b study in patients with HER2-

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Table 4
Incidence of adverse events of special interest.

	Arm A Trebananib 10 mg/kg QW + Paclitaxel + Bevacizumab $n = 56$	Arm B Trebananib 3 mg/kg QW + Paclitaxel + Bevacizumab $n = 57$	Arm C Placebo + Paclitaxel + Bevacizumab $n = 58$	Arm D Trebananib 10 mg/kg QW (Open-label) + Paclitaxel $n = 57$
Adverse events of interest, %				
Edema	56	60	29	70
Grade ≥ 3	2	4	3	7
GI perforation/abscess	0	2[a]	2[b]	0
Hemorrhagic events	51	68	55	23
Grade ≥ 3	0	4	2	0
Hypokalemia	2	5	7	2
Grade ≥ 3	0	4	0	0
Impaired wound healing	2	0	3	0
Grade ≥ 3	0	0	2	0
Infusion reactions[c]	11	9	10	2
Proteinuria[d]	4	4	2	4
Pulmonary embolism	0	2	2	0
Grade ≥ 3	0	2	2	0
Venous thromboembolic events	7	9	3	2
Grade ≥ 3	5	5	3	2
Ascites[c]	4	2	3	0
Pleural effusion	5	7	0	9
Grade 3	0	2	0	0
Blurred vision[c]	7	4	3	0

[a] Grade 3 gastroinestinal perforation.
[b] Grade 2 perirectal abscess.
[c] No grade ≥ 3.
[d] No grade ≥ 3; assessed as an adverse event.

positive locally recurrent/metastatic breast cancer (ClinicalTrials.gov, NCT00807859).

Although there are some known overlapping toxicities among the three agents administered, there was little evidence that any of the combinations resulted in a toxicity profile worse than that described for these agents in monotherapy or in combination with chemotherapy. Peripheral edema occurred more frequently among patients receiving trebananib, consistent with previous studies of trebananib both alone [14], and combined with chemotherapy [15,17,24]. In contrast with a previous phase 2 ovarian cancer study [17], the incidence of hypokalemia was not increased among patients receiving trebananib. In general, the incidence of AEs associated with VEGF pathway inhibitors [25], including hemorrhage, proteinuria, and hypertension, was similar in Arms A, B, and C, and the incidence of grade ≥ 3 events appeared consistent with those reported for patients receiving bevacizumab plus paclitaxel in the E2100 study [8]. Notably, hemorrhagic events and hypertension occurred more frequently among patients who received blinded bevacizumab with or without trebananib (ie, those in Arms A, B, and C) compared with those who received open-label trebananib (ie, those in Arm D). These results suggest that trebananib did not increase the incidence of these AEs. There were more venous thromboembolic events in Arms A and B (7% and 9%, respectively) than in Arm C (3%); however, these numbers are small and few patients had grade ≥ 3 events. Three other specific AEs of interest, recently associated with trebananib treatment, are worth mentioning: ascites and pleural effusion [24,26]; and blurred vision risk. In the present study, the incidence of these events was low, and there was only one grade ≥ 3 event (grade 3 pleural effusion). Although these AEs appear to be associated with trebananib treatment, reasons for their onset remain unknown. Overall, toxicity was manageable, and the incidence of AEs of any grade, AEs grade ≥ 3, and serious AEs was similar across the treatment arms. If further studies of trebananib are conducted in patients with breast cancer, it will be crucial to more thoroughly characterize the predisposition, onset, duration, impact on quality of life, and response to management of edema and other AEs associated with trebananib treatment.

The estimation study design limited the assessment of the treatment effect. However, the results were anticipated to inform the design of future studies rather than demonstrate statistically significant improvements in outcomes between treatment arms [27]. It should also be noted that while treatment in Arms A, B, and C was blinded, treatment in Arm D was open-label, which may have influenced the investigators' assessments of efficacy and toxicity outcomes.

Conclusion

In this phase 2 estimation study, there was no prolongation of PFS with the addition of trebananib (3 or 10 mg/kg) to bevacizumab and paclitaxel at the doses tested. Toxicity of each of the regimens was consistent with prior experience with each of the treatment components. Data from the exposure-response analyses support additional studies in locally recurrent or metastatic breast cancer of trebananib plus paclitaxel at doses > 10 mg/kg.

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Authors' contributions

VD, HW, JJ, LYD, J-PG, PB, SAH, AG, GR, SAL, GJ, KCL, HR, PS-R, TP, MÁSP, and DS participated in data collection. AL performed statistical analyses. Y-NS performed pharmacokinetic analyses. CAP and DJS contributed to the design of the study. All authors participated in data interpretation and in drafting the manuscript or revising it for intellectual content. All authors read and approved the final version of the manuscript.

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Conflict of interest statement

VD and J-PG have received honoraria from Amgen Inc. SAL has received research funding from Amgen Inc. HW has been a consultant to and received honoraria from Amgen Inc. GJ has been a consultant to and received honoraria and research funding from Amgen Inc. HR has received honoraria from Bristol-Myers Squibb. SAH has received funding and travel reimbursement from Roche/Genentech. TP has received honoraria and research funding from Roche. DJS has received research funding from and is a stockholder in Amgen Inc. AL, YNS and CAP are employees of and stockholders in Amgen Inc. JJ, LYD, PB, AG, GR, KCL, PS-R, MÁSP have no conflicts to declare.

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Abbreviations

AE	adverse event
AUC_{ss}	area under the concentration–versus–time curve at steady state
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
CT	computed tomography
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
HR	hazard ratio
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
Q2W	every 2 weeks
QW	once weekly
RECIST	Response Evaluation Criteria in Solid Tumors
VEGF	vascular endotheilial growth factor

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